

Editorial

SARS, Xenotransplantation and Bioterrorism: Preventing the Next Epidemic

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Experience is a wonderful thing. It enables you to recognize a mistake when you make it again. (Apocryphal Yiddish Proverb)

Introduction

The worldwide outbreak of severe acute respiratory syndrome (SARS) has focused attention on the unpredictability of outbreaks of novel infectious diseases. In part, such outbreaks are the unavoidable consequence of global air travel, poverty, urban crowding, and incursions into ecologically remote regions. The inability to detect such outbreaks early in their course is the result of *the absence of a coordinated international program for the detection and reporting of, and response to, potential epidemics*. The failure of health authorities to publicize possible outbreaks often appears to reflect misguided efforts at governmental public relations rather than prevention of public panic.

Opinion is divided as to why the international community is repeatedly 'surprised' by the emergence of new pathogens or epidemics. One view is that these outbreaks are simply 'bad luck' and that the effects of such an outbreak are unavoidable. An alternate view is that an 'early detection system' might recognize new pathogens and generate rapid responses that might blunt the impact of such outbreaks. Outbreaks of infection have been the result of the development of new viral species (e.g. influenza strains), human infections due to pathogens normally restricted to other species (e.g. Ebola or possibly xenotransplantation) or bioterrorism (e.g. anthrax).

The World Health Organization (WHO) sponsors a surveillance program which monitors influenza strains worldwide. The justification is simple. Major influenza pandemics have occurred approximately every 25 years. The worldwide influenza pandemic of 1918–19 ('Spanish flu') killed up to 50 million people worldwide. WHO estimates that the next flu pandemic might cause over 2 million hospitalizations and 650 000 deaths within 2 years in the developed world alone. As for many infections, the impact of influenza is greatest in immunocompromised populations – the elderly or malnourished, those with cardiopulmonary disease, and those with immune defects or receiving immune suppression. However, the impact of pandemics is *greatest in developing regions*.

The roles of nonhuman reservoirs of infection are relevant to many such outbreaks. Influenza viruses are natural pathogens of birds, swine and humans. Pigs become infected with human and avian influenza in addition to swine viruses. Outbreaks of influenza occur when multiple viruses from different species infect swine simultaneously, genetic reassortment (mixing) occurs, and a new virus with new virulence features and novel surface epitopes (antigenic shift) emerges. Novel strains emerge every few years – chicken flu, swine flu, Hong Kong flu, and this year's H7N7 avian flu in the Netherlands. Without vaccination, no immunity exists in people exposed to these new strains via contact with animals, and influenza spreads rapidly. Surveillance identifies the new strains and, prior to each outbreak, vaccines are developed for the predominant new strains. With an outbreak, animals thought to be reservoirs of disease are sacrificed and vaccine is available to combat the spread of infection. New mutant strains do not generally develop during an outbreak, and the vaccines generally remain effective on an annual basis.

How does SARS compare with influenza? Thus far, SARS has resulted in 8403 probable infections with 775 deaths [WHO data as of June 5, 2003 (1)]. Special features of this outbreak are worth noting. Like influenza, coronaviruses infect many animal species. Coronaviruses mutate rapidly – changing surface epitopes. This has already occurred with the SARS coronavirus, and makes the development of effective vaccines extraordinarily difficult. Consider that no effective vaccines for the 'common cold' (largely rhinoviruses and coronaviruses) exist. Coronaviruses inhibit respiratory epithelial ciliary function – enhancing susceptibility to bacterial superinfection and pneumonia. SARS

has spread rapidly as a nosocomial infection, affecting physicians, nurses and hospital staffs as well as community contacts of infected individuals. This reflects the stability of the virus in the environment, with spread by contamination of surfaces, hands and clothes.

Is SARS unique? The value of reporting and surveillance systems becomes evident when considered in the light of a series of recent epidemics.

In the summer of 1976, an unknown respiratory illness struck guests at a hotel in Philadelphia; a similar outbreak was subsequently recognized among patients at a major hospital. This epidemic defined Legionnaires' disease, due to a bacterium *Legionella pneumophila* and spread by contaminated water droplets in air ducts (2,3). This rapidly progressive pneumonia was particularly severe in the elderly and in those individuals with pre-existing lung disease or immune deficits. Many required mechanical ventilation; some died.

In the same year, an outbreak of a severe, often-fatal viral hemorrhagic fever (due to Ebola virus, one of two members of a family of RNA viruses called the Filoviridae) was detected in Africa and has appeared sporadically since. Researchers believe that the virus is zoonotic (animal-borne) and is normally maintained in an animal host native to the African continent. People can be exposed to Ebola virus by contact with blood or secretions of an infected individual.

In 1979–81, an outbreak of severe *Pneumocystis carinii* pneumonia and rare types of cancer were reported by doctors in Los Angeles and New York among gay male patients. This was recognized as the harbinger of an epidemic of an immune deficiency disorder, now defined by HIV infection and AIDS.

In 1993, a rapidly progressive respiratory infection carried by rodents was discovered in New Mexico and the Four Corners region of the United States. This zoonotic illness was characterized as Sin Nombre Virus infection and Hantavirus Pulmonary Syndrome. Illness including fever and muscle aches is followed by shortness of breath and coughing and often progresses rapidly, necessitating hospitalization and mechanical ventilation.

In the mid-1990s, concerns were expressed that the transplantation of organs from nonhuman species as a therapy for humans with organ failure (xenotransplantation) would allow novel infectious agents to move from these immunosuppressed individuals into the general human population ('xenosis or xeno-zoonosis'). A moratorium was placed on such transplants in many countries. Subsequently, a series of potential pathogens have been investigated in donor swine, including a novel porcine endogenous retrovirus (PERV), as well as porcine cytomegalovirus and porcine lymphotropic herpesvirus (4,5).

In 2001, a series of patients with rapidly progressive respiratory failure were identified in the United States as the victims of attacks with spore-forming bacterium *Bacillus anthracis* (the agent of anthrax) (6). These were recognized as bioterrorist attacks belatedly, and only in the context of the terrorist attacks of 9/11/01. Anthrax is a zoonotic disease that occurs in wild and domestic mammals (e.g. cattle, sheep, goats, camels, antelope, and other herbivores). *B. anthracis* spores can remain viable in the soil for many years. Humans can become infected with *B. anthracis* from infected animals.

Since 2001, human metapneumovirus has been identified as a major cause of respiratory infection in children and the elderly, causing pneumonia, bronchiolitis and bronchospasm. This virus has been associated with severe pneumonia in immunocompromised individuals after stem cell transplantation in Europe and the United States (7).

In 2002, a series of individuals developed West Nile Virus (WNV) meningoencephalitis (WNVME) after receiving blood transfusions or organ transplants from donors infected with this virus. Humans are accidental hosts for WNV, which is carried by mosquitoes and migrating birds. Once infected, individuals may be asymptomatic or minimally symptomatic (headache) following viremia.

In 2003, a severe acute respiratory infection (SARS) emerged from Asia, thought to be due to a novel coronavirus (8). In contrast to prior infections, this infection appears to be marked by high infectivity (efficient person-to-person spread) and has resulted in respiratory failure and deaths in affected individuals. It has been hypothesized, but not yet confirmed, that this virus was a zoonotic infection derived from rats, birds, swine or other animals (civets) used as food sources in Asia. Consistent with the observations of Kumar et al. in this issue (9), this infection has taken a particular toll on the elderly, those with underlying pulmonary disease, and in immunocompromised hosts.

What Are the Lessons of This Series of Outbreaks?

First, infectious disease epidemics occur fairly frequently around the world. This is not a problem of a single nation or geographic region, particularly in an era of routine air travel. These infections are increasingly derived from zoonotic sources as we alter the ecology of the world in which we live. Zoonotic infections may gain in virulence as they 'adapt' to new, accidental, hosts such as humans.

Second, the impact of SARS, or other outbreaks, cannot be measured only in terms of lives lost, hospital beds filled, or job time missed. Affected regions have suffered tremendous economic injury and reallocation of limited financial resources to emergency healthcare. The impact

of outbreaks may be greatest in transplantation. Transplant recipients are the sentinels for common pathogens in the environment – either in regions of high endemicity (e.g. tuberculosis, histoplasmosis, *Trypanosoma cruzi* in parts of South America) or during outbreaks of infection (e.g. West Nile Virus or SARS coronavirus). This becomes a barrier to the performance of transplant procedures when infection may be transmitted by blood transfusions or with transplanted tissues. *In the absence of sensitive, rapid and accurate microbiologic assays for screening of cadaveric donors in a timely fashion, transplantation may cease for the duration of the epidemic.* This is a reasonable, if unfortunate, precaution. With clinical disease overwhelming medical facilities and filling ICU beds, even elective surgery is reduced, eliminating living organ donation also. In Canada, there have been 218 probable cases with 31 deaths (as of June 4, 2003). In Toronto, a single student with possible SARS caused an entire school to close; over 8000 individuals were quarantined. Two allograft recipients have died. One liver recipient is reported in this issue (9), and the other was in a rehabilitation center recovering after lung transplantation 4 months earlier.

Finally, although the response by international health authorities to the SARS outbreak was quite rapid, epidemiologic investigations were delayed by the lack of timely information provided by local health authorities. On February 11, 2003, the Chinese Ministry of Health reported to the World Health Organization that 305 cases of an acute respiratory syndrome of unknown etiology had already occurred in six municipalities in Guangdong province in southern China between November 16, 2002 and February 9, 2003. Of note, in the weeks before the outbreak gained international attention, some physicians were receiving reports of this syndrome from contacts in Hong Kong, Singapore, and China via the Internet. It is not possible to know whether earlier action on the part of health authorities might have interrupted the progress of this epidemic.

What can be done? The recognition of the extent of an outbreak by public health officials and honest dissemination of information are essential. Such information may allow individuals to seek medical attention if indicated and to reduce exposure to uninfected persons. (For full case definitions for SARS, see the WHO and CDC websites, www.cdc.gov/ncidod/sa and www.who.int/csr/sars) Physician education will enhance screening and triage of possible cases of SARS. However, the key to successful management of epidemics is the determination of who is infected. *It is essential that widely available, rapid, accurate, highly sensitive and low-cost assays be available for screening of possibly infected individuals and for epidemiologic surveys.* Assays for the SARS-associated coronavirus are now available. In an epidemic, the early availability of such diagnostic tools provides a critical advantage. Without such assays, it is not possible to determine the optimal allocation of resources (financial

and medical) to fight infection. With such assays, appropriate measures (quarantine, negative-pressure hospital rooms, therapies for other infections, sacrificing of infected animals) may be instituted in a timely fashion.

How do we develop assays or vaccines in a timely manner, in advance of new outbreaks? One possible approach is to develop worldwide screening and reporting systems for novel infections, both in patients and in animals. One focus of such surveillance is the sentinel population of immunosuppressed patients after organ or stem-cell transplantation or after cancer chemotherapy. Such patients provide a fertile ground for most types of pathogens. *We do little, however, to take advantage of these highly susceptible populations to track 'unusual infectious events' that may indicate the start of the next epidemic.* Cooperative systems that exist are hindered by the absence of resources, incompatibility of data sets or computer systems, or lack of political will to assure compliance. For xenotransplantation, some governments concerned about the potential introduction of unknown or unrecognized infections from other species into immunocompromised humans require specimen archiving, incident reporting and tracking of contacts. For bioterrorism, such tracking is, for all we know, cloaked in the intelligence community until outbreaks occur – and deaths result. ***Meaningful distinctions do not exist for the medical community between epidemics caused by natural causes, new technologies or bioterrorism.*** One international surveillance system would serve us all. Such surveillance could utilize newer molecular techniques (e.g. broad-range polymerase chain reaction primers, oligonucleotide microarrays, or representational difference analysis) to recognize novel molecular species (potential pathogens).

As clinicians, we cannot reasonably screen each potential donor of blood, hematopoietic stem cells, or whole organs for every possible human pathogen. Rapid diagnostic tools are not yet available for many potential pathogens; the optimal techniques are not universally available. We compromise, appropriately, using medical histories, routine laboratory assays, and a series of microbiologic assays to exclude potentially fatal donor-derived infections such as HIV or hepatitis B and C. In endemic regions or in donors from such areas, additional screens are added for *Trypanosoma cruzi* (Chagas' Disease), leishmaniasis or strongyloidiasis. A useful screening tool has been proposed by Kumar et al. for use in the SARS outbreak in Toronto (9). Occasionally and unfortunately, despite such screens, infection may be transmitted and then amplified in immunocompromised transplant recipients. In general, given the odds, we do surprisingly well in avoiding such donor-derived infection.

International collaboration to share data on infections would provide a window of opportunity to limit the impact of future epidemics. After centuries of experience with

epidemics large and small, the commendable investigative skills of the WHO, CDC and other national and international health agencies remain handcuffed by the lack of cooperation and by governmental policies. As we fail to coordinate infectious disease reporting on an international basis, outbreaks will continue to occur and we will always be a little bit too late.

And with the next outbreak, we will, once again, be surprised.

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